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Synthesis of 1,2,3-Triazole 5-Chloroisatin Derivatives via Copper-Catalyzed 1,3-Dipolar Cycloaddition Reactions

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Abstract— *A facile and simple protocol for the 'Click' cycloaddition of organic azides with N-propargylchloroisatine catalyzed by CuI, produces in good yields novel of 1,4-disubstituted 1,2,3-triazoles were obtained. Compared to the uncatalyzed cycloaddition, the yields are significantly improved in the presence of CuI as catalyst, without alteration of the selectivity. The regio- and stereochemistry of the cycloadducts has been corroborated by ^{1}H, ^{13}C NMR spectroscopy.*

Keywords— Click cycloaddition, CuI, 1,4-disubstituted 1,2,3-triazoles, ^{1}H NMR, ^{13}C NMR.

I. INTRODUCTION

One of the research activities of our laboratory in the domain of heterocyclic chemistry deals with the 1,3-dipolar cycloaddition of nitrile oxides and azides as dipoles across the double or triple bonds of dipolarophiles [1–3]. A very recent example is the 1,3-dipolar cycloaddition of nitrile oxides to the allyl group of 1-allyl-5-chloro-indole-2,3-dione providing a series of isoxazolines [4]. This versatile strategy for the synthesis of heterocyclic compound is more and more used in materials chemistry, drug discovery, and chemical biology [5–7]. The synthesis of 1,2,3-triazoles is well-known and has been thoroughly studied, since the conception of "click chemistry" by Sharpless and co-workers [8]. In fact, the orthogonal character vs. the reactivity of most functional groups, complete regioselectivity in favor of the 1,4-disustituted-1,2,3-triazole, mild reaction conditions, and easy installation of the required azide and terminal alkyne moieties in the reactive partners, render the metal-promoted version of the long-standing Huisgen 1,3-dipolar cycloaddition reaction the most prominent technique in the click-chemistry toolbox [9].

With applications ranging from material science to medicinal chemistry the 1,2,3-triazole core has been recognized as one of the most potent azoles with broad chemotherapeutic properties including antifungal [10], anticancer [11], antitubercular [12], antimalarial [13], anti-inflammatory [14], and antiviral [15] activities. Isatin and its derivatives are currently being considered as an important class of molecules, since many of them show diverse biological activities such as antiviral, anticancer [16–19], antibacterial [20, 21] and anticorrosive [22, 23] ones [24].

In view of the importance of these classes of products, we have designed a new class of 5-Chloroisatine derivatives via 1,3-dipolar cycloadditions under non-catalyzed thermal activation in ethanol in the presence of the simple and inexpensive catalysts $CuSO_4$ between an azide and 5-chloro-1-(prop-2-ynyl)indoline-2,3-dione.

II. EXPERIMENTAL DETAILS

2.1. Synthesis of 5-chloro-1- (prop-2-ynyl) indoline-2,3-dione as a dipolarophile:

The synthesis of 5-chloro-1- (prop-2-ynyl) indoline-2,3-dione is given by the reaction of 5-chloro-1*H*-indole-2,3-dione (0.2g ,1,1mmole), with 1.2 eq of propargyl bromide using dimethylformamide (15 mL) as solvent, under the conditions of phase transfer catalysis in the presence of K_2CO_3 (0.23 g, 1.16 mmol) and a TBAB catalyst (0.035 g, 0.10 mmol), at room temperature, then the mixture was evaporated under reduced pressure, the residue reaction was treated and the product was purified on a silica gel column (eluent: ethyl acetate/hexane) [25-31].

5-chloro-1-(prop-2-ynyl)indoline-2,3-dione **(1):** yield: 93% ; mp:166-170 °C; R_f= 0.78 (ethyl acetate / hexane: 1/2); ^{1}H NMR ($CDCl_3$) δppm 7.57-7.62(m, 2H, H_{Ar}) ; 7.12(d, H, H_{Ar} ,J=6Hz); 4.54 (s, 2H, CH_2); 2.34 (t, H, J=3Hz). ^{13}C NMR ($CDCl_3$) δppm :181.55(C=O) ; 156.60 (N-C=O) ; 147.87, 130.07,118.50 (Cq) ; 137.80, 125.24, 112.75 (CH_{Ar}) ;73.72(C≡C) ;71.21(CH); 29.59(CH_2) .

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2.2. GENERAL PROCEDURES FOR THE CLICK SYNTHESIS OF 1,2,3-TRIAZOLES 1A-3A:

To a stirring solution of equimolar amounts of azides and 5-chloro-1-(prop-2-ynyl) indoline-2,3-dione dissolved in Ethanol and water (1:1), $CuSO_4$ (0.5 eq) and Na-ascorbate (1eq) were added. Stirring was continued for 6–10 hours at 25°C, until the consumption of the starting material as indicated by thin layer chromatography (TLC), and then the crude was extracted with ethyl acetate and dried over sodium sulfate. Removal of the solvent in vacuum gave the desired 1,2,3-triazole derivatives **1a–3a** which were crystallized from ethanol.

***1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-chloroindoline-2,3-dione*:(1a):** yield: 89%; mp: 140-145°C; R_f=0.57 (ethyl acetate / hexane: 1/4). ^{1}H NMR ($CDCl_3$; 300MHz) δppm 7.32-7.29 (m, 2H, H_{Ar}); 7.26 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.08 (d, 2H, H_{Ar}, $^4J_{H-H}$ =3Hz); 6.99-7.03 (m, 1H, CH); 6.71-6.73 (d, 2H, H_{Ar}, $^4J_{H-H}$ =3Hz); 6.47-6.49 (m, H, H_{Ar}); 5.23 (s, 2H, CH_2); 4.89 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$; 75MHz) δppm: 186.50 (C=O); 165.30 (N-C=O); 149.82, 143.25, 135.62, 130.53, 117.81 (Cq); 132.65, 131.15, 129.47, 127.66, 123.11 (CH_{Ar}) 125.65 (CH); 56.54, 43.82 (CH_2).

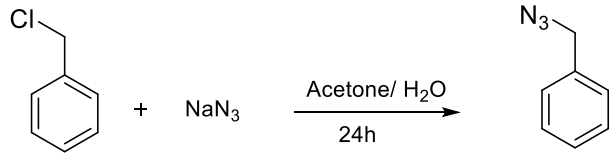
***5-chloro-1-((1-decyl-1H-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione* (2a):** yield: 87%; mp: 130-135°C; R_f=0.55 (ethyl acetate / hexane: 1/4).. ^{1}H NMR ($CDCl_3$; 300MHz) δppm 7.51(m, H, H_{Ar}); 7.48-7.49 (m, 2H, H_{Ar}); 7.29 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 4.94(m,2H, CH_2); 4.26(t, 2H, CH_2, $^3J_{H-H}$ =9Hz) ; 1.78-1.82(m, 2H, CH_2) ; 1.17 (m, 14H,CH_2), 0.83(t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$; 75MHz) δppm: 183.53 (C=O); 164.88 (N-C=O); 147.28, 143.89, 130.32, 111.66 (Cq); 135.40, 130.11, 124.81 (CH_{Ar}) 123.11 (CH); 53.36, 45.09, 32.80, 29.61, 28.56, 27.07, 22.83 (CH_2)16.47 (CH_3).

***5-chloro-1-((1-dodecyl-1H-1,2,3-triazol-4-yl)methyl)indoline-2,3-dione* (3a):** yield: 85%; mp: 135-138°C; R_f=0.53 (ethyl acetate / hexane: 1/4). ^{1}H NMR ($CDCl_3$; 300MHz) δppm 7.51 (m, H, H_{Ar}); 7.46-7.49 (m, 2H, H_{Ar}); 7.27 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 4.94 (s, 2H, CH_2); 4.23(t, 2H, CH_2, $^4J_{H-H}$ =3Hz); 1.80 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz) ; 1.17(m, 18H, CH_2) ; 0.78 (t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$; 75MHz) δppm: 181.62 (C=O); 161.27 (N-C=O); 147.91, 143.67, 114.42 (Cq); 134.98, 130.95, 122.69 (CH_{Ar}); 123.32 (CH); 51.87, 45.30, 37.88, 29.82, 29.61, 28.58, 27.70, 22.83 (CH_2); 17.95 (CH_3).

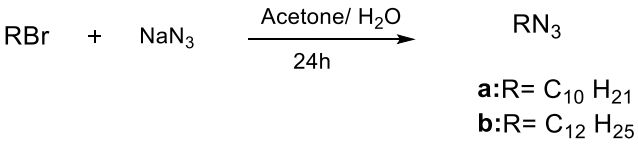
III. RESULTS AND DISCUSSION

3.1. Synthesis of azides:

Azides are considered to be very important compounds in industry and in biological application. The azide derivatives have been used in rubber vulcanization, to produce polymers, dyes, foam of plastics, drugs, pesticides and herbicides [32]. Many azide compounds have mutagenic activities [33-34]. The chemistry of azides has therefore attracted the attention of many chemists, then many of the azide compounds play an important role in organic chemistry [35, 36]. One of the most useful synthetic applications of the azides is the preparation of 1,2,3-triazoles by the 1,3-dipolar cycloaddition reaction of the azides with substituted alkenes. The method of synthesis of benzyl azide and the other azides adopted in the course of our work is borrowed from loubinoux et al. [37]. It involves the action of benzyl chloride/monohalogenated chains on sodium azide in water/ethanol.



Scheme 1



Scheme 2

3.2. Cycloaddition of copper-catalyzed alkyne-azide (CuAAC):

As one of the best click reactions to date, the copper-catalyzed azide-alkyne cycloaddition features an enormous rate acceleration of 107 to 108 compared to the uncatalyzed 1,3-dipolar cycloaddition. It succeeds over a broad temperature range, is insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography or recrystallization [38].

The principle of this reaction is the use of the copper (I) salts which can be generated from Cu (I) salts or Cu (II) salts using sodium ascorbate as a reducing agent to catalyze the cycloaddition reaction between an azide and an alkyne makes it possible to obtain 1,4-disubstituted 1,2,3-triazole exclusively and considerably reduces the reaction time and temperature. The use of copper (I) as a catalyst gave rise to the copper-catalyzed 1,3-dipolar azide/alkyne cycloaddition (CuAAC) which satisfies many of the criteria stated by Sharpless [39, 40].

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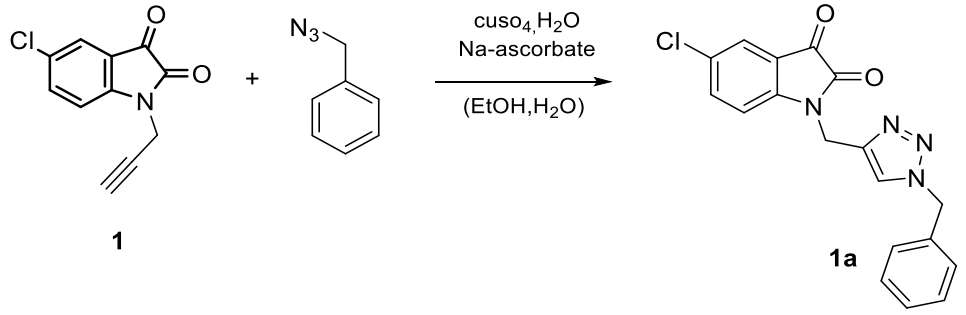
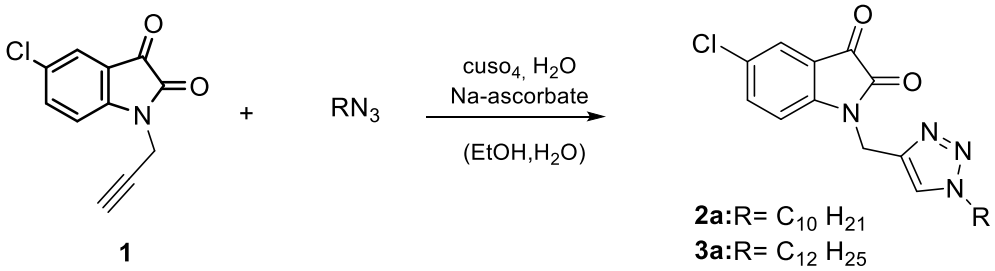


Scheme 3



Scheme 4

IV. CONCLUSION

In summary, we have developed a new and efficient method for the synthesis of novel 1,2,3-triazole-substituted with higher yields were obtained with a significant reduction in the reaction times. The process involves regiospecific cycloaddition between a propargylic alkyne and azides using CuI as simple commercially available catalysts in ethanol at 25°C.

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